A Network Model for Alzheimer's Disease

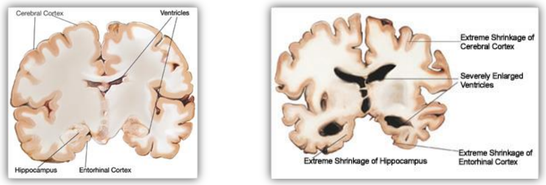
C. Rose Kyrtsos[1,2] and John S. Baras[1,2,3]

University of Maryland, (1) Dept. of Bioengineering, (2) Institute for Systems Research, (3) Dept. of Electrical Engineering

Abstract We have derived a multiomic network model to study the relationship between cholesterol and Aβ *in silico* to integrate with future experimental work. A pseudo-metabolic network approach has been taken to model the interactions between various signaling molecules, carrier and transport proteins, as well as other proteins that are considered pertinent to AD pathogenesis.

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the most common form of dementia among the elderly in the US today, affecting 1 in 8 individuals over the age of 65. AD is not merely memory loss, but also leads to changes in personality, loss of voluntary motor control, poor spatial reasoning, and general loss of a good quality of life. Drastic , pathological changes in brain structure are often seen in patients in later stages of the disease, leading to a decrease in the total volume of the brain; significant loss of synapses and neurons, specifically in the hippocampus and cortical regions; widespread inflammation; and deposition of the beta amyloid protein as diffuse or oligomeric plaques.

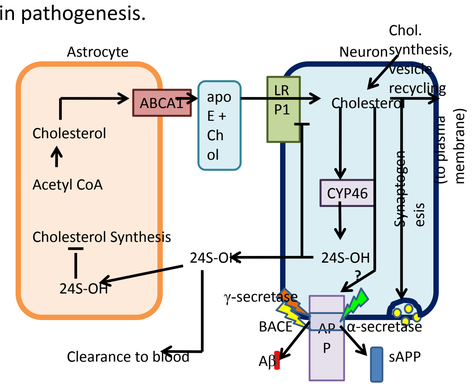


Brain Anatomy in AD: Healthy (left) versus AD (right) brain morphology. Adapted from (1).

Cholesterol Link?

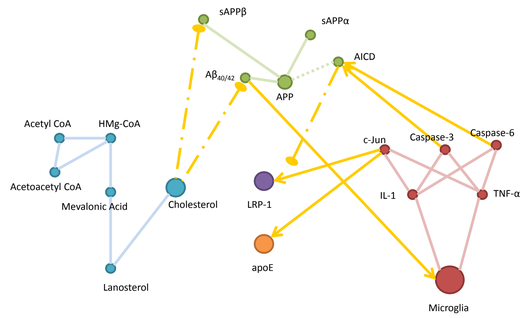
The brain contains the highest level of cholesterol of all organs in the human body (~25%). The majority of this cholesterol (~80%) is necessary for producing myelin, the specialized lipid layer that insulates axons and allows for the proper conduction of action potentials. Cholesterol is also necessary for maintenance of plasma membrane fluidity, synaptic vesicle and synapse formation, and neurite extension (Bjorkhem 2004).

In AD, the level of cholesterol in both the blood plasma and the brain is believed to play a role in pathogenesis. Within the blood, high cholesterol levels due to hypercholesterolemia or heart disease have been shown to lead to an increased deposition of beta amyloid plaques (Refolo 2000, Pugielli 2003). A study by Liu et al in 2007 demonstrated that increased levels of APP led to a decrease in LRP-1 expression and cholesterol levels, with an increase in apoE expression levels (Liu 2007). This correlates with what is seen in patients with AD: low LRP-1 expression levels at the blood-brain barrier and brain cholesterol levels when compared to healthy controls (Donahue 2006). To complicate our understanding further, Halford & Russell did crossed AD mice with mice that had been knocked out for cholesterol hydroxylase (an enzyme necessary for cholesterol synthesis), and demonstrated that AD mice with low brain cholesterol showed no statistical change in beta amyloid levels or plaque densities (Halford & Russell 2009). Further research needs to be completed to better understand the role that cholesterol may play in pathogenesis.



Cholesterol & Aβ: Relationship between cholesterol and Aβ processing in the brain that has been used in our model.

Simplified Network Model



Model Background & Description of Topological Network

There are numerous metabolic pathways that are involved in the normal function of the brain, and even more that are involved in neurodegenerative processes such as inflammation and apoptosis. The basic model that we have developed here focuses on the generation and clearance of beta amyloid, the biosynthesis of cholesterol, inflammation due to secretion of interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα) by microglia, activation of apoptosis by caspase-3 and -6, as well as the purported roles of apoE and LRP-1 in beta amyloid and cholesterol processing in the brain.

Network Equations

We have created a system of ODE equations to model our metabolic network, taking into account interactions only between the most important molecules. In our model, APP levels are constant with respect to time:

$$\frac{dAPP}{dt} = 0$$

We made this assumption since we are studying late onset AD where there is currently no evidence that demonstrates that increased APP production is part of the disease. Only 5% of APP is cleaved into soluble APPβ via β-secretase (BACE) cleavage, the first step in the production of Aβ:

$$\frac{dsAPPB}{dt} = 0.05[APP][BACE] - k_1[cholesterol][APP]$$

The second term describes the inhibition of BACE activity by APP (Crameri 2006). The concentration of BACE has also been standardized to 1 to simplify the model further. Beta amyloid levels are modeled as the difference between generation and degradation:

$$\frac{dA\beta}{dt} = k_2[sAPPB][\gamma sec] - d_1$$

where d1 is the rate of degradation of Aβ, given as:

$$d_1 = [Rate\ by\ microglia] + [Rate\ by\ IDE\ or\ NEP] + [Clearance\ rate\ by\ LRP - 1]$$

Generation of AICD is via caspase activity on the portion of APP remaining after Aβ cleavage, while degradation most likely occurs through processing by the lysosomal pathway:

$$\frac{dAICD}{dt} = k_3[sAPPB][caspase] - k_{11}[AICD][LRP] - d_1$$

Production of the inflammatory cytokines IL-1 and TNF-α by microglia in response to increasing levels of Aβ are given by the following equations:

$$\frac{dIL1}{dt} = k_4[\#microglia]\left[\frac{rate}{time}\right]$$

$$\frac{dTNF\alpha}{dt} = k_5[\#microglia]\left[\frac{rate}{time}\right]$$

where k_4 and k_5 represent the strength of Aβ as a promoting factor in microglial release of IL-1 and TNF-α, the # of microglia are the number present in the entire system, and the rate per time is the number of molecules produced per unit time. The cholesterol level is given as:

$$\frac{dchol}{dt} = k_6[HmgCoA] - k_1[cholesterol][APP]$$

where k_6 is the net production rate of cholesterol, dependent on both the generation rate via Hmg-CoA reductase and the inhibition by binding to APP. Both apoE and LRP-1 production are promoted by IL-1 and TNF-α, and have a basal transcription rate as well:

$$\frac{dapoE}{dt} = k_7[IL1] + k_8[TNF\alpha] + BR$$

$$\frac{dLRP}{dt} = k_9[IL1] + k_{10}[TNF\alpha] + BR - k_{11}[AICD][LRP]$$

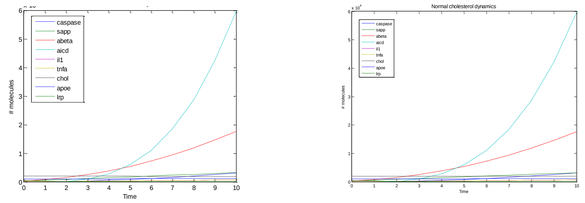
where BR represents the basal transcription rate and the ki's represent the strength of the interaction. The final term in the LRP expression represents the loss of LRP-1 due to inhibition by AICD. Caspase copy number is directly related to the level of IL-1 and TNF-α:

$$\frac{dcaspase}{dt} = k_{12}[IL1] + k_{13}[TNF\alpha]$$

Simplified Model Results

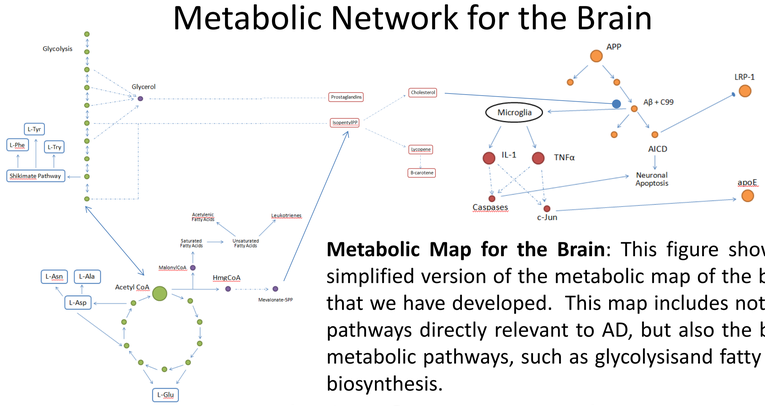
Analysis and Simulation Methods

Equations have been modeled using Matlab. Initial concentrations and reaction rates have been estimated. Future simulations will need a much more accurate method to assign realistic weights to the edges, as well as ascertain that all interactions between molecules have been accounted for. A simulation with 10 steps was performed.



Results: Comparison of the effect of decreased cholesterol synthesis on Aβ processing. (top) Normal cholesterol synthesis; (bottom) Reduction of cholesterol synthesis. There is only a very minor variation between the rise time for the apoE and LRP-1 molecules. Further simulations need to be performed with more accurate edge weights.

Metabolic Network for the Brain



Metabolic Map for the Brain: This figure shows a simplified version of the metabolic map of the brain that we have developed. This map includes not just pathways directly relevant to AD, but also the basic metabolic pathways, such as glycolysisand fatty acid biosynthesis.

Conclusion & Future Work

We have developed a simplistic model for the metabolic network of the brain containing pathways that are pertinent to AD. A system of ODEs was developed to describe the network and analyzed in Matlab using approximated rate constants. Our results were not very significant given the inaccuracy of the rate constants used, yet the model shows promise to be improved as we gather experimental data from *in vivo* experiments that we are currently conducting. These experiments are testing how decreased cholesterol in the brain affects the processing of beta amyloid, as well as the expression levels of apoE and LRP-1. We are also focusing on the contributory role that inflammation may play in the observed decrease in brain cholesterol in AD patients. We have also started development of a more complex model for the brain metabolic network encompassing not only those pathways directly relevant to AD, but also the basic metabolic networks of the brain.

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Acknowledgements

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